Final Action Cover Sheet
Bristol-Myers Squibb Position Paper
Comments on Regulatory Actions

Name of Regulation/Guidance: "Draft guidance for Industry on NDA's: Impurities in Drug Substance		
Type of Submission: 99 APR 15 A9:16		
To PhRMA	☐	PhRMA Comment Due Date:
To FDA	x	FDA Comment Due Date: April 21,1999

Overview/Summary:
This draft guidance was published on January 21,1999(Docket No.98d-1267;Federal Register/Vol.64,No.13) recommends that the ICH Guideline on Impurities (dated March 30, 1995) that applies to new drug substances, should also apply to NDAs, supplements and Type II DMF's involving a drug substance that is NOT considered new. The new rule would have an impact everytime changes in the synthesis or process of the drug substance not considered new are presented in a filing.
Also affected would be NDA's submitted for new dosage forms of previously approved drug products, and for combination drug products whose components already have their individual approvals.
As the "ICH Guideline on Impurities" spells out recommendations on identification, qualification and reporting/specification, the drug substance in a new formulation of a marketed older product would have to satisfy the guideline, with the possible consequences of replacing older methods, or perhaps even impurity structure determination, or specification revision.
The draft guideline could impact lifecycle management in the sense that older CMC packages could no longer just be referenced.

Request:	
Return to: H.Leon Levinsky	Return By (date): March 29,1999
Approved By: Robert L Simon	Not Approved By:
Date Approved: 3/26/99	Date Rejected:
If not approved, please explain:	
Other Comments:	
Dr. L.Smaldone L Smaldone L. Csillan	CC: Joan Kenney

98D-1267

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March 26,1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 98D-1267; "Draft Guidance for Industry on NDA's: Impurities in Drug substances", (Federal Register/Vol.63, No.13, January 21,1999)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA draft guidance for industry on NDAs: Impurities in Drug Substances.

We commend the US FDA for:

1. Recognizing that recent developments in analytical chemistry and instrumentation make it possible to better measure and control the level of impurities in drug substances and synthesis intermediates; with the result that application of new technology can enhance drug substance and drug product quality.

2. Seeking to provide regulatory relief to drug substance manufacturers by harmonizing the US FDA requirements with those of the international (ICH) community.

3. Seeking to apply the same regulatory requirements to "new' and "old" drug substances.

We agree, in principle, with the FDA that it is appropriate to apply the ICH *Q3C Impurities in Drug Substances* standards for "new" drug substances to "old" drug substances. Never the less, we

recommend that:
(Cont.)

1. There be a transition period following publication of the final guidance that allows manufacturers sufficient time to develop and validate assay/impurities test methods for their "old" drugs, and to set appropriate limits for specified impurities and degradation products – based on historical data and manufacturing capability.

2. Consideration be given to the fact that significant capital investment is required for laboratory instrumentation and training, and for development of validated test methods. This could be a burden for very small companies, and also for manufacturers who produce a large number of compounds.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie F. Smaldone
Senior Vice President
Worldwide Regulatory Affairs

SPH12

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